THE CHINA CONNECTION

CHINA-BORN, U.S.-TRAINED SCIENTISTS ARE HELPING FOSTER INNOVATION AND REVITALIZE RESEARCH IN THEIR NATIVE LAND.

BY ROBERT KOENIG
ILLUSTRATION BY MIKE PERRY

Tian Xu taps a button on his remote control and looks up at the 4-foot-wide screen on his office wall at the Yale School of Medicine. The image that flickers on—showing a desktop stacked with files and half-finished diagrams—could be any scientist's cubicle. Except that the scene is 7,400 miles away, in China.

Xu pokes at the control to swivel a distant webcam and focus on the face of a scientific collaborator, Xiaohui Wu, a mouse researcher at Fudan University in Shanghai. "This is fantastic," says the bespectacled Xu, testing the sound level as he prepares for a teleconference. "It's like I'm sitting in Shanghai."

There's good reason for Xu to be in Shanghai—both virtually and in person. In addition to his duties as an HHMI investigator in Yale's department of genetics, he is a cofounder of the Institute of Developmental Biology and Molecular Medicine at Fudan, one of China's leading biomedical research universities. Xu's work at those two laboratories, half a world apart, aims to give scientists valuable research tools to help reveal the genetic underpinnings of many human diseases.

The around-the-world arrangement—under which Xu spends about one of every four weeks teaching and researching in China—is also an innovative step toward closer collaboration with scientists in a nation that lagged behind North American research for most of the 20th century and lost many of its talented young researchers to the West.

Today, China is catching up, in part by attracting expatriates like Xu who are willing to work at least part time to help improve the quality of Chinese research. Their personal stories vary, but many share the feeling that it is time to "give back" to their native land, which—after decades of stagnation—is poised to become a major international player in biomedical research. As China expands its laboratories and begins to adopt successful templates of Western science, many experts see the potential for more synergy among biomedical researchers in the two countries.

"I see science as very much a global enterprise," says HHMI President Robert Tjian, a biochemist who left Hong Kong as a young child with his parents and, after a brief time in South America, has since lived in the United States. "If the American style of science can be disseminated to other places, it can only be good—especially in the field of medicine."

The Fudan institute combines a Western model of research with a Chinese cost structure (see "Bold Move," page 29)—a template that Xu says is needed to help spur innovation in China's research.

"China has a tremendous number of smart young people who are interested in pursuing science, and its recent economic growth has made it possible to invest heavily in science and technology research," he says. "What China needs now are role models in innovative science."

Researchers and students who work with him, both in China and in New Haven, describe Xu as such a model. "He is creative, highly focused, and a great mentor," says Yale postdoc Sheng Ding, who first studied under Xu in Shanghai.

The story of how Xu became a role model is emblematic of the changing perspectives of expatriate Chinese scientists over the last 30 years. The former "black sheep" of his Jiaxing high school has become an American mentor for a new generation of bright young science students in a Chinese city that has become a window to the West.

FOLLOWING OPPORTUNITIES ABROAD

With an impish grin, Xu admits that he spent his unhappy high school years in Jiaxing playing "Go"—a Chinese strategic board game. "I liked the game

Dustin Aksland

because you win if you are good," he says. "It doesn't matter where your ancestors came from."

Unlike the Go meritocracy, Xu's privileged family history made him "a targeted kid" during the Cultural Revolution, from 1966 to 1976, which was hard on intellectual families like Xu's. His father, a teacher, was demoted to a labor camp; his mother was punished as a "capitalist roader"—someone with left-leaning political views who bows to bourgeois pressures. And Xu was mistreated by his school principal because he came from a politically tainted family.

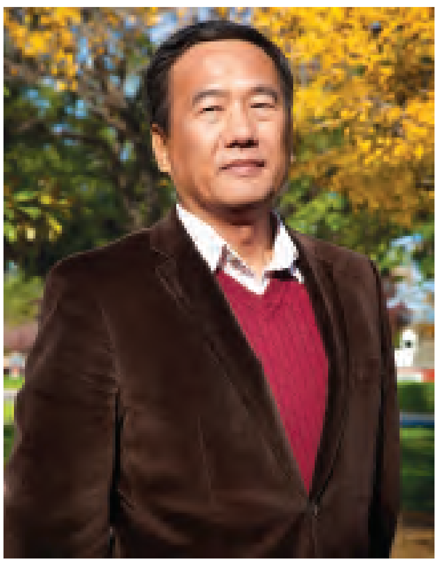
The Cultural Revolution was only the latest blow to Chinese science, which had been damaged by the wars, political upheavals, and social turmoil of the 1930s and 1940s and then restructured along the Soviet model after the communist takeover in 1949. That ossified system—under which most research took place in Academy of Science institutes rather than at universities—became vulnerable to political favoritism, corruption, and domination by seniority. Then, starting in the late 1960s, Chairman Mao Zedong's "Down to the Countryside" campaign transplanted urban "young intellectuals" to rural areas, destroying the careers of many promising scholars who might have pursued science.

If the severe academic disruption had continued beyond 1978, Xu might never have attended college. But his application to Fudan University coincided with China's reform movement that restored merit-based admissions to universities. "Fudan really changed me," says Xu. "The level of research was not high then, but the *spirit* of scientific exploration was tremendous."

That spirit may have been uplifting, but Xu and other Chinese undergraduates discovered that, to do first-rate science, they had to pursue their Ph.D.s abroad. After he met a visiting official from the City College of New York, Xu was accepted in the college's graduate program in biology. In 1983, the young student—who spoke virtually no English—arrived at a ramshackle house in Harlem with $50 in his pocket and the challenge of living in New York for a school year on a stipend of $1,500.

Many Chinese expatriates share similar stories. "At that time, China was not a good place to study life sciences," recalls molecular biologist Min Han, a HHMI investigator at the University of Colorado at Boulder, who has been Xu's main collaborator in establishing the new institute at Fudan.

Sent to a farm during the Cultural Revolution, Han majored in biology at Beijing (Peking) University and was recruited to study in the United States—getting his Ph.D. from the University of California, Los Angeles—as part of a program created by the late Ray Wu, a Cornell University biologist who played a key role in recruiting Chinese students to U.S. universities during the 1980s and 1990s. Another talented scientist recruited in the same program was Xiaodong Wang, now an HHMI investigator at the University of Texas Southwestern Medical Center at



left page: Yang Dan and Mu-ming Poo, University of California, Berkeley

right page: (top) Tian Xu, Yale School of Medicine; (bottom, l-r) Xiaodong Wang, University of Texas Southwestern Medical Center at Dallas; Min Han, University of Colorado at Boulder

Xu: Chris Jones Wang: Matt Rainwaters Han: Carmel Zucker

Dallas. Wang recalls the "incredible culture shock" of his move from Beijing to Texas in 1985.

Even if they were not directly affected by the Cultural Revolution, many younger Chinese science students also headed to the United States because "you didn't stay in China if you wanted a career in research," says neuroscientist Yang Dan, an HHMI investigator at the University of California, Berkeley. After she'd earned her initial degree in physics at Beijing (Peking) University, Dan was restricted by the rigid Chinese system from doing graduate studies in another field, so she decided to pursue a life sciences Ph.D. program at Columbia University in New York, where she had to work hard to catch up on basic biology and related courses that she had missed in Beijing.

Despite the sometimes difficult transitions, many of those students succeeded with the help of talent, hard work, and American mentors. "We were nurtured and cultivated by our professors," recalls Xu, who landed a fellowship at Yale within a year of his arrival in New York and was soon using fruit flies as a model organism to decipher the roles of genes in neural development.

Excited by his early success, Xu called his mother in China and explained that he was making a name for himself in America by studying flies. After a long pause, she said: "Son, we have lots of flies right here in our hometown."

EMULATING THE WEST

On the corner of Xu's desk sits a stack of books about famous American medical innovators. "I want to see how this country built up biomedical research," he says, looking for a template for potential reforms in China.

In the field of medical research, Xu sees parallels between pre-World War I America and today's China. A century ago, while the United States was becoming a world power, its universities and biomedical research lagged behind Europe. Thousands of young Americans went to Britain, Germany, and France for their graduate or medical studies and to learn the research techniques of the great European masters.

Eventually, American university innovators—including pathologist William H. Welch, who built the Johns Hopkins University School of Medicine into a research powerhouse, and Abraham Flexner, whose 1910 report led to fundamental reforms of U.S. medical schools—combined lessons from Europe with their own ideas to create what has become the world's leading biomedical research complex.

"Like America in those years, China is on the cusp of great advances in science and technology," says Xu. "One of my dreams is to set up a new university in China that would teach innovation and would be modeled on some of the most effective research institutions in the West."

Before that happens in China, however, plenty of work needs to be done. In the meantime, numerous initiatives are under way to deepen scientific ties between China and America. After China began to reform its economy, the nation stepped up its efforts to convince top expatriate scientists to return home. In 1998, the education ministry's Changjiang Scholars Program started offering incentives for expatriates to do research and to teach at universities in China. After many targeted researchers in the United States said they had little interest in returning to China full time, the program was altered in 2006 to include some senior scientists on a part-time basis.

In 2009, China's central government started an ambitious program called *Qianren Jihua*, or the Thousand-Person Plan. The goal is to recruit as many as 2,000 top Chinese-born scientists, financial experts, and entrepreneurs back to China over the next decade.

One of the most influential U.S.-trained scientists who has announced plans to return permanently to China is Wang, who plans to move to Beijing this summer as he begins his second stint—after 5 years in a part-time, long-distance capacity—as the director of China's National Institute of Biological Sciences. The institute started from scratch a few years ago under a mostly Western model and now boasts 23 labs and 500 scientists—nearly all its principal investigators did their Ph.D. and/or postdoc work in the United States.

Wang says he has reached a point in his life "when it's time to give back" to his native country. "And there are great opportunities in China today." Xu expresses similar sentiments about his inner need to help young scientists in China—especially out of gratitude to his early inspiration to professors at Fudan, who "opened up a new world of science for me."

For her part, Dan has become involved in the past 5 years in research collaborations with neuroscientists in Shanghai and has been mentoring young scientists there and at Berkeley. "A lot of really good expatriate scientists are trying to revamp the research structure at Chinese universities," she says. "The idea is to more strongly link teaching and research."

In addition to university reforms, similar efforts are being made to bolster Chinese Academy research, including an innovative initiative led by Dan's husband, neuroscientist Mu-ming Poo, who is also based at University of California, Berkeley. Born in China, Poo began his university studies in Taiwan and later excelled in the United States. Asked by Academy officials to assess neuroscience research in China, he advised them in 1999 to create an entirely new institute to avoid "the flawed mechanism of managing China's established scientific institutions … [which] left little room for innovation." Poo became the founding director of the Chinese Academy's Institute of Neurosciences, which

BOLD MOVE

It took a leap of faith for Tian Xu to move from Shanghai to Harlem in 1983, but he says the biggest risk he has taken during his career was switching a decade ago from fruit flies to mice as model organisms to study gene functions. ¶ *Xu had made his* name at Yale and later as a postdoc at HHMI Vice President Gerald M. (Gerry) Rubin's lab at the University of California, Berkeley, for his *Drosophila* research—conducting large-scale analyses of mutant flies to decipher the roles of key genes and the biochemical pathways related to cancer cell growth and metastasis. ¶ *But when Xu applied* for an HHMI investigator position in 1996, he made a bold proposal: he would discover a way to create mutant mouse strains as easily as developing mutant flies. That would represent a big step forward in genetic screening of mice, about 99 percent of whose genes have direct equivalents in the human genome. ¶ *"It was risky* because I had a lot to learn about mouse genetics," Xu recalls, describing the years of complex and often frustrating research that it took for him to come up with the deceptively simple breakthrough: using a moth transposon ("jumping gene") called *piggyBac*. Inserted into the mouse genome, the tiny segment of DNA causes random mutations when the animal breeds, disabling one gene per mouse and creating an efficient way to create knockout mutants. ¶ *"Geneticists had been searching* for decades to find a system like this for mammals—an efficient tool for transgenesis and mutagenesis," says Xu, who displays a framed cover of the August 2005 issue of the journal *Cell* that featured his *piggyBac* report. "Now we have the tool and we need to produce the mutant mice strains for scientists to use in their research." ¶ *With the new technique,* scientists can produce the mutant mouse strains about 100 times faster and cheaper than they could with previous methods. And Xu says the Institute of Developmental Biology and Molecular Medicine at Fudan University in Shanghai, which he coestablished at the urging of Chinese officials, is able to produce such strains at a lower cost than a similar facility in the United States. ¶ *At the Fudan institute,* which already houses 25,000 mouse cages, Xu and his researchers so far have produced about 5,000 strains of knockout mice. The goal is to produce 100,000 mutant strains by the end of 2010, among which scientists hope to eventually identify knockout equivalents for nearly all of the 25,000 or so genes in the mouse genome. ¶ *"I wanted to accomplish things* with a real impact on society," says Xu. "To do that, you need to take some risks along the way." *—R.K.*

is producing high-quality research. He receives no salary and "works only on scientific aspects" of the institute, while retaining his faculty and research position at Berkeley.

"I think it's a very positive trend," says HHMI's Tjian. "These scientists have a sense of responsibility to their native country and it's clear that China is progressively expanding its scientific presence."

ENGAGING A COMMON GOAL

While the current trends in Chinese science are mostly headed in the right direction, expats say it will take time—as well as a continued government commitment to reform the research system—to reach the nation's potential. In the meantime, many of the older generation of China-born scientists prefer to keep their research bases in the United States.

Xu says he didn't really want to start a new institute at Fudan but was convinced to proceed because "it was a priority for the Chinese. I like it because the research is connected with a university, which is unusual for China." With the advent of teleconferencing and high-speed Internet in China, he finds that he can "accomplish our goals with fewer trips back and forth" between New Haven and Shanghai.

Like his Fudan institute colleague, Han opted—for family as well as professional reasons—to limit his China commitment, despite entreaties from Chinese officials to move back. "I regard the U.S. as my main base for research," he says, "but that doesn't mean that you can't make contributions to Chinese science."

Han says, "I see changes in both directions—good and bad" in Chinese science. For example, the dramatic increases in the number of Chinese science students are placing heavy burdens on faculty. "Every lab tends to have way too many students. And there are serious ethics problems that result from the pressure to produce lots of papers."

Wang is optimistic as he prepares for his move to Beijing, saying that China's economic success is freeing up tremendous resources for research. "Young people have an easier time getting grants in China today than in the U.S.," he says. Also, those students "treat scientific research as a privilege. If a merit-based system takes root, these young people will get great opportunities and excel."

Poo agrees that, "as more scientists return to China after successful postdocs in the U.S., the quality of Chinese research will continue to improve." But

(continued on page 48)

CONTINUED FROM PAGE 29
(THE CHINA CONNECTION)

he cautions that "the new traditions of high-quality science have yet to become established at most of the Chinese research institutes. My concern is that most institutions need to move more quickly in the direction of merit-based resource allocation and promotion. Rigorous review of the research performance of individual scientists rarely happens, and the outcome of the reviews, if they were carried out, rarely has any consequence."

While Xu believes that far more progress needs to be made, he is generally optimistic about China's "tremendous potential" in science. "Scientific interaction is one of the best ways to deepen the understanding between China and America," he says, looking up at his teleconference screen with its live connection to his colleague in Shanghai. They are discussing how to expand the Fudan institute's research and offer its unique mouse mutants to scientists worldwide who are trying to understand and find cures for diseases.

"This is a site where East meets West," he says. "We are engaged in a common goal: to develop knowledge as a way to improve the well-being of humankind." ■

CONTINUED FROM PAGE 33
(A MATTER OF EQUILIBRIUM)

For other diseases, though, the culprit is the equilibrium between the fission and fusion of a different organelle: the mitochondrion.

Mitochondria, energy-generating organelles, snake throughout the insides of cells in an interconnected network. "People often think of mitochondria as static organelles that work alone," says HHMI investigator David Chan, "but they constantly fuse and divide. No one really understood why these events happen, or how, until the last 10 years."

Chan, at the California Institute of Technology, studies how the cell achieves a balance in its mitochondria network. If fusion overwhelms fission, the mitochondria become excessively long and connected, eventually "collapsing into a messy jumble," says Chan. And if fission overwhelms fusion, the organelles are dramatically fragmented and less efficient at producing energy. It's a delicate balance.

When geneticists at Duke University linked a mitochondrial fusion gene to a neurological disease, Chan wondered how a defect in mitochondrial fusion might lead to peripheral neuropathy, which causes numbness and weakness in the hands and feet. Chan engineered mice that lacked the implicated fusion gene, *mitofusin2*. He found defects in the mitochondria of the Purkinje cells, a class of neurons in the brain known for the dramatic fan of fibers that branch off them. With crippled mitochondrial fusion machinery, the arbor of fibers was reduced to short stumps.

Looking closer at the mitochondrial membranes, Chan saw fragmented organelles, not the interconnected network that ought to be there. Furthermore, mitochondria usually contain their own DNA—mtDNA. "But in this fragmented mutant, only a fraction of them have mtDNA," Chan says. The observation of missing DNA explains why fragmented mitochondria can't produce energy—they lack the DNA that encodes proteins controlling energy generation. Neurons may be particularly sensitive to these defects, because the cells are among the most energy demanding. His lab is pursuing the link between mitochondrial fission and fusion and mtDNA, since mtDNA defects are associated with additional pathological conditions.

On a computer screen, when membrane fission and fusion are slowed down, they appear to be straightforward processes. Press play and the membranes move. The merging of membranes looks fluid and natural, like it requires no molecular machinery at all. After all, two soap bubbles can join together without the help of proteins. But inside the cell, as these researchers have shown, taking away a piece of the membrane's control mechanisms leads to a messy jumble of membranes, or a stand-still in vesicle creation—and both problems have unmistakable links to disease. ■

WEB EXTRA: To learn what happens when vesicles arrive at their targets and how structural biology is illuminating the biology of vesicles, visit www.hhmi.org/bulletin/feb2010.